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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/976,613	10/12/2001	Lawrence A. Rheins	DERM1100-7	4301

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EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	9

DATE MAILED: 06/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/976,613	RHEINS ET AL.	
	Examiner	Art Unit	
	Zachary C Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-12 are pending in the instant application.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

In instant application, the first sentence of the specification claims priority to U.S. Application 09/375609 but there is no statement that the instant application is a divisional of U.S. Application 09/375609.

Objections

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The current title "Method for detection of biological factors in the epidermis" is not descriptive because there are no claims directed to methods of detection of biological factors. The claims are all directed to a method of identifying a compound which causes a dermatitis.

Claim Objections

Claim 9 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 9 does not further limit the polynucleotides of claim 1 because there are no nucleotides other than DNA or RNA that encode cytokines.

Double Patenting

Applicant is advised that should claim 6 be found allowable, claim 7 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention 2) state of prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working templates, 6) breadth of claims, 7) amount of direction of guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(a) Claims 1-12 are drawn towards identifying a compound which causes dermatitis by detecting the quantity of polynucleotide encoding a cytokine. The specification (in Tables 2 and 3) teaches that the ratios of IL-4, IL-8, and IL-13 mRNA to GADPH are detected at a higher level after 48 hours of allergen exposure, than are detected after 72 hours of irritant exposure, or in normal skin. Therefore, in order to identify a compound which, for example, causes for example, ACD in a subject, these mRNA must necessarily be quantitated after 48 hours of exposure. However, while applicants disclose the quantity of these mRNAs after 72 hours of irritant exposure, there is no disclosure of the quantity of these mRNA after 48 hours of irritant exposure.

Due to the high level of unpredictability in the art (set forth in the following paragraph) suggesting several other IL mRNA levels can rise and fall over time after allergen exposure, and in the absence of other evidence suggesting IL-4, IL-8, or IL-13 mRNA levels are stable over time after exposure, it is not predictable what the levels of these mRNAs will be after 48 hours of irritant exposure. To use the instantly claimed method would require undue experimentation to determine if the 48 hour time point is diagnostic, and if so, what levels of IL-4, IL-8, or IL-13 mRNA would be diagnostic.

The teachings of Kondo (reference AN cited in the IDS of 11/20/2002) indicate that the levels of epidermal cytokine mRNA vary significantly over time following exposure to an allergen or irritant. In particular, Kondo teaches that in mice, ACD was characterized by an initial suppression in IL-lα levels followed by an increase in 1L-1α mRNA levels at 12 to 24 hours following exposure to hapten and that IL-1β, IL-6, 1L- 10 and GM-CSF mRNA levels did not increase until 6 hours after exposure to a hapten. In addition, Kondo teaches that in ICD, 1L-1 mRNA levels were upregulated 1 hour following exposure to a hapten, but then were suppressed 3-24 hours following exposure. Furthermore, Kondo teaches that at 24 hours following exposure to a hapten IL-1β, IL-6, IL-l0 and GM-CSF mRNA levels were increased in both ICD and ACD, and thereby levels of these cytokines at 24 hours could not be used to distinguish between ICD and ACD. Kondo teaches (page 372) that it is important to select the appropriate time points and to look at the entire time course of the reaction to elucidate markers to differentiate ACD and ICD. Grangsjo (reference AB cited in the IDS of 6/09/2003) also highlights the unpredictability in the art of detecting the level of cytokine as indicative of response to irritants in that Grangsjo reports that the cytokine response in ICD may be

time and substance dependent. Specifically, Grangsjo found that nonanoic acid (NAA), but not SLS induced an increase in IL-6 mRNA levels, whereas SLS, but not NAA, induced an increase in GM-CSF levels.

(b) Claims 1-12 are further not enabled in a manner commensurate in scope with the claims because they encompass the detection of DNA. While the prior art appreciates the detection of RNA, specifically mRNA as an indicator of expression of cytokines (or other proteins), the DNA that is transcribed to make the mRNA would not be expected to be present in any different quantity when the gene is expressed, as opposed to when it is not. It is not accepted in the art that cytokine expression happens via DNA amplification; rather the DNA is transcribed to make mRNA, which is translated to make protein. Amplification (the production of protein in an amount disproportionate to the amount of DNA present) can happen either at the transcription or translation step, and often at both, but not by DNA amplification. Accordingly, since the person of ordinary skill in the art would not accept that DNA levels would be indicative of cytokine expression, and as the specification provides no guidance nor working examples of such, the specification is not enabling of detection of DNA for diagnosis or distinguishment of inflammatory reactions or any other disorder not directly associated with a change in the DNA itself.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 8, and 10-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because the claim encompasses indicating a dermatitis by detecting a polynucleotide encoding any cytokine, but the specification is directed only to indicating dermatitis by detecting polynucleotides encoding the cytokines IL-4, IL-8, and IL-13.

Claim 1 is also indefinite because the recitation "a section of skin" encompasses all skin, which will contain all nucleotides encoding all cytokines, in the genome of the cells. Accordingly, the method is incomplete and non-functional. The claims do not set forth a comparison which levels are compared to a control or reference value.

Claims 2-5 are indefinite because it is unclear how these claims further limit the method of claim 1. Claims 2 and 3 seem to pre-ordain the outcome, making the method moot. For all four claims, what method steps are implied by the further limitation?

Claim 8 is indefinite because it is unclear how the step relates to the method of claim 1. It is unclear at what point during the method of claim 1 that polynucleotides will be isolated from the skin.

Claim 10 is indefinite because it is unclear how the step relates to the method of claim 9 (and claim 8 and claim 1). It is unclear at what the point during the method that the step recited in claim 10 will be performed.

Claim 10 is also indefinite because the recitation "...wherein an elevated amount of IL-4 is indicative of ACD" fails to specify sufficient method steps to distinguish ACD. It is not clear whether an elevated amount of IL-4 mRNA is in reference to normal skin

cells, or skin cells exhibiting an ICD reaction. The claims do not set forth a comparison step in which levels are compared to a control or reference value. Claims 11-12 are similarly indefinite. Also, they are unclear because, to use claim 10 as an example, it is not clear as to whether the applicant is referring to the amount of IL-4 polynucleotide or protein. In regard to this matter, claim 10 would be definite if Applicant amended the portion of the claim to read, "...wherein an elevated amount of mRNA encoding IL-4 is indicative of ACD". Claim 11 is indefinite for the same reason but would be made definite if Applicant amended each claim to read "...wherein the amount of mRNA encoding IL-4 or IL-8 is indicative of ICD." Claim 12 is indefinite for the same reason but would be made definite if Applicant amended the claim to read "...wherein an increase of mRNA encoding IL-8 in the absence of mRNA encoding IL-4 is indicative of ICD."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fischer, U.S. Patent 4,836217 (Jun. 6, 1989) in further view of Paludan (reference AH cited in the IDS of 4/14/2003).

Fischer teaches (in column 1, lines 18-26) "in the epicutaneous testing procedure, the substance suspected to have allergenic or irritant properties is applied to

normal skin under occlusion for a certain period of time, this application being effected in a controlled manner and with a suitable formulation and concentration of the test substance. This will then in the contact allergy cases, produce an allergic eczema in the test area. Irritant substances give rise to irritative eczema reactions of a similar character..." The term "eczema" is synonymous with the term "eczema dermatitis" and eczema is therefore a form of dermatitis. Thus Fischer teaches a method of identifying a compound which causes dermatitis, comprising contacting a section of skin with the compound under conditions which would induce dermatitis. Fischer does not teach diagnosis of dermatitis by detecting a polynucleotide encoding a cytokine, or the further limitation of claim 8 that the polynucleotides are isolated from the skin.

Paludan teaches diagnosis of ACD by quantitating a polynucleotide encoding IL-8. Specifically, Paludan teaches quantitation of IL-8 cytokine mRNA by a "quantitative PCR method" and that an allergic skin reaction is characterized by an elevated quantity of IL-8 mRNA over normal skin (see Table II). The method used by Paludan (detailed on page 830) involves obtaining epidermal samples by scraping the skin. This isolated epidermal sample contains the polynucleotide (IL-8 mRNA) quantitated by Paludan.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the method of identifying a compound which causes dermatitis taught by Fischer with the cytokine mRNA detection taught by Paludan. The person of ordinary skill in the art would have been motivated to make that modification because the type of dermatitis (allergic or irritant) is not distinguished in the patch testing taught by Fischer while Paludan teaches (on page 834, column 2) that their technique is "useful for discriminating

between epidermal IL-8 mRNA levels in a variety of inflammatory skin diseases and reactions (Fig 5, Table II) and should be applicable to analysis of other cytokine mRNAs and other skin compartments."

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pistoor (1996, American Journal of Pathology, 149(10): 337-343) in further view of Paludan (reference AH cited in the IDS of 4/14/2003). Claims 6 and 7 are dependent on claim 1 and recite the limitation that "...the skin is contacted *in vitro*".

Pistoor teaches (pages 337-342) an in vitro assay using cultured human skin to determine whether a compound is an allergen, irritiant, or neither. In this assay, the cultured human skin is contacted in vitro with the compound to be tested. Pistoor does not teach detecting a polynucleotide encoding a cytokine to indicate dermatitis. As described above, Paludan teaches quantitative PCR to detect IL-8 cytokine mRNA and the quantity of IL-8 mRNA indicative of allergic and irritative dermatitis.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the method of identifying a compound which causes dermatitis by contacting skin with the compound in vitro taught by Pistoor with the cytokine mRNA detection taught by Paludan. The person of ordinary skill in the art would have been motivated to make that modification because Paludan teaches (on page 830) that PCR "amplification is an extremely powerful technique for the analysis of small samples" and that it is the "most

sensitive method of detection for specific mRNAs" and (on page 834) "that the sampling techniques have the advantage of being rapid", and in the absence of other evidence, quantiting IL-8 mRNA would provide an equivalent determination of whether a compound causes dermatitis as the diagnostic method of Pistoor, and using the method of Pistoor would provide the benefit of not contacting an organism with a compound *in vivo*.

Claims 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fischer, U.S. Patent 4,836217 (Jun. 6, 1989) in view of Paludan (reference AH cited in the IDS of 4/14/2003) and further in view of Asada (Journal of Investigative Dermatology Asada (April 1997. Journal of Investigative Dermatology. 108(4):406-411).

As taught above, Fischer and Paludan teach all of the limitations of claim 9. Paludan further teaches (in Table II) the quantity of IL-8 mRNA that is indicative of allergic contact dermatitis, irritant contact dermatitis, and normal skin. Fischer in view of Paludan does not teach that an elevated amount of IL-4 is indicative of ACD, the amount of IL-4 indicative of ICD, or that an increase in IL-8 in the absence of IL-4 is indicative of ICD.

Asada teaches, in the abstract, "isolated mRNA from dispase-separated epidermis and dermis of ... naïve BALB/c mice at various times after TNCB challenge. Changes in ... IL-4 mRNA levels (by semiquantitave RT-PCR) were more reproducible and dramatic than those of other cytokines studied." On page 408, Asada teaches that 1% TNCB causes nonspecific inflammatory changes in

naïve mice. On page 409, Asada uses the expression "nonspecific (irritant) reactions", indicating the terms are being used equivalently in this reference. The nonspecific inflammatory changes in naive mice do not include a change in IL-4 mRNA (Figure 1A, IL-4 box, -/T columns). An elevation in IL-4 mRNA is observed in the allergic response observed in sensitized mice (Figure 1A, IL-4 box, T/T columns). In summary, Asada shows that IL-4 mRNA is not induced in response to an irritant contact reaction and that IL-4 mRNA is elevated in response to an allergic contact reaction.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the method of identifying a dermatitis-inducing compound taught by Fischer with the method of cytokine IL-8 mRNA detection taught by Paludan, and furthermore, in light of the teachings of Asada, to quantitate IL-4 mRNA in place of, or in addition to, quantitating IL-8 mRNA. The person of ordinary skill in the art would have been motivated to make that modification because Paludan teaches (on page 834, column 2) that their technique is "useful for discriminating between epidermal IL-8 mRNA levels in a variety of inflammatory skin diseases and reactions (Fig 5, Table II) and should be applicable to analysis of other cytokine mRNAs" and because Asada has provided the quantity of IL-4 mRNA necessary to provide as reliable a diagnosis of ACD or ICD as quantitation of IL-8 mRNA and which would be useful in confirming results obtained with IL-8 mRNA.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary L Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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